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Original Article

Goserelin combined with bicalutamide improves immune function and inflammatory response in patients with advanced prostate cancer

Qingling Xie[1], Lijuan Zeng[1], Wenzheng Wu[2], Chenglin Xiao[2]

[1]Department of Urology, The Fifth Affiliated Hospital of Guangzhou Medical University, Guangzhou 510700, Guangdong Province, China; [2]Department of Urology, The Second Affiliated Hospital of Guangzhou Medical University, Guangzhou 510260, Guangdong Province, China

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Abstract: This study aimed to investigate the effect of goserelin combined with bicalutamide on the immune function and inflammatory response in advanced prostate cancer patients. From January 2017 to January 2019, 122 prostate cancer patients were selected as the research participants. Among them, 54 receiving intermittent therapy with goserelin and bicalutamide were included in group A, and 68 receiving continuous treatment with goserelin and bicalutamide were included in group B. The effects of the two treatment methods on the patients' clinical efficacy, safety, pain, immune function, and inflammatory factors were analyzed. The VAS scores of those in group A at 1 month, 6 months, and 12 months after they started taking the medication were significantly lower than those in group B ($P<0.001$). The $CD4^+/CD8^+$ levels of those in group A were significantly lower than those in group B at 6 months and 12 months after they started taking the medication ($P<0.001$). The $CD4^+$, $CD8^+$ and $CD3^+$ levels in group A at 6 months and 12 months after they started taking the medication were significantly higher than those in group B ($P<0.001$). The TNF-α, IL-1β, and IL-6 levels of those in group A treated for 6 months and 12 months were significantly lower than the corresponding levels in group B ($P<0.001$). There was no significant difference in the PSA and F-PSA levels between those in group A treated for 1 month, 6 months, and 12 months ($P>0.05$). There was no significant difference in the incidence of gynecomastia, breast tenderness, diarrhea, nausea, temporary liver function changes, kidney stones, osteoporosis, anemia, or other adverse reactions in either group ($P>0.05$). The total effective rate of group A was 94.44%, and the total effective rate of group B was 70.59%. The total effective rate of group A was significantly higher than the rate of group B ($P<0.05$). Goserelin combined with bicalutamide improves the clinical efficacy of intermittent therapy for advanced prostate cancer patients, increases their immune function, and relieves the body's inflammatory response.

Keywords: Goserelin, bicalutamide, prostate cancer, treatment

Introduction

Prostate cancer refers to an epithelial malignancy with abnormal hyperplasia of the acinar cells in the prostate [1, 2]. Its morbidity ranks 6th among male malignances and increases with age and seriously threatens men's health [3, 4]. Clinically, radical treatment can be adopted for patients with prostate cancer diagnosed early. However, due to the relatively hidden nature of prostate cancer, early clinical diagnoses are rare. When prostate cancer patients are diagnosed, most of them are in the late or advanced stages. Radical surgery does not achieve better efficacy [5-8]. Endocrine therapy is the main treatment for hormone-sensitive advanced prostate cancer patients. It can prevent the further development of prostate cancer by inhibiting the physiological action of androgens [9, 10].

Goserelin and bicalutamide are commonly used endocrine therapy drugs. Goserelin is a gonadotropin-releasing hormone agonist, administered parenterally, which inhibits the production of estrogen and androgen and reduces the production of testosterone [11, 12]. Bicalutamide, a non-steroidal antiandrogen drug, antag-

onizes androgens by competitively binding the corresponding receptors of androgens [13]. At present, some clinical studies also show that goserelin and bicalutamide can interfere with the proliferation of tumor cells in prostate cancer patients [14]. However, the effect of goserelin combined with bicalutamide on improving the immune function and the body's inflammatory response in patients with advanced prostate cancer is still controversial [15].

This study aims to discuss the effect of goserelin combined with bicalutamide on the immune function and the body's inflammatory response in patients with advanced prostate cancer from the perspective of the efficacy and safety of endocrine therapy.

Methods and materials

Data and methods

Altogether 122 patients diagnosed with prostate cancer in the Second Affiliated Hospital of Guangzhou Medical University from January 2017 to January 2019 were selected as the research participants. The patients receiving intermittent therapy with goserelin and bicalutamide were included in group A, and they were (66.00±9.00) years old on average, with an age range from 62 to 80. Those who received continuous treatment with goserelin and bicalutamide were included in group B, and they were (67.00±9.00) years old, with an age range from 61 to 83. There were 68 patients in group A and 54 patients in group B. Inclusion and exclusion criteria: (1) Only patients with prostate cancer diagnosed and treated at the Second Affiliated Hospital of Guangzhou Medical University were included, all referring to the diagnostic criteria for prostate cancer of the World Health Organization [16]. (2) The patients with contraindications to the drugs used in this study, those with hypertension, hepatitis B virus, gallstones, AIDS, various blood diseases or other diseases, and those suffering from mental diseases or cognitive dysfunction were excluded. The participants and their families signed informed consent forms in advance. This study was approved by the Ethics Committee of the Second Affiliated Hospital of Guangzhou Medical University and it is in line with the Declaration of Helsinki.

Mode of administration

The patients in group A received intermittent therapy with goserelin and bicalutamide and goserelin (approval number: SFDA approval no. J20160091; AstraZeneca Pharmaceutical Co., Ltd., registration standard for imported drugs JX20010474) was injected subcutaneously into the anterior abdominal wall with a specification of 3.6 mg once every 28 days. They took bicalutamide orally (approval number: SFDA approval no. H20073877; Zhejiang Haizheng Pharmaceutical Co., Ltd.) Dosage was 50 mg/time, once a day, once every 4 weeks. We reviewed the patients' PSA levels every month and suspended the medication when their serum PSA <0.2 ng/ml. When their PSA >0.4 ng/ml, we resumed the medication. The patients in group B received continuous treatment with goserelin and bicalutamide, and goserelin was injected subcutaneously into the anterior abdominal wall with a specification of 3.6 mg once every 28 days. The bicalutamide was taken orally, 50 mg/time/d, and both groups were treated for 12 months.

Outcome measures

The pain relief rates and the VAS [17] scores of the two groups were compared. The changes in the immune function-related indexes of the patients in both groups were also compared ($CD3^+$, $CD4^+$, $CD8^+$ lymphocyte subsets were determined using the immunoenzyme staining technique). The changes in the inflammatory reaction-related indexes in both groups were observed (tumor necrosis factor (TNF-α), interleukin-1β (IL-1β), interleukin-6 (IL-6)) and were determined using an enzyme-linked immunosorbent assay. The prostate-specific antigen (PSA) and free PSA (F-PSA) levels were compared between the two groups. The drugs' side effects, the adverse reactions, and the treatment efficacy in both groups were compared [18].

Enzyme-linked immunosorbent assay

The TNF-α, IL-1β and IL-6 expression changes were measured using enzyme-linked immunosorbent assays. The serum was separated using a centrifuge at 3500 r/min, and then it was stored in a freezer at -20°C for later use. The tests were carried out in strict accordance

Table 1. General clinical data of the patients in both groups

Group	Group A (54)	Group B (68)	t/X^2	P
Age	66.00±9.00	67.00±9.00	0.610	0.543
Average body weight (Kg)	70.50±4.30	69.90±5.00	0.700	0.485
Place of residence			0.373	0.542
Countryside	24 (44.44)	34 (50.00)		
Cities and towns	30 (55.56)	34 (50.00)		
Smoking			0.182	0.670
Yes	40 (74.07)	48 (70/59)		
No	14 (25.93)	20 (29.41)		
Drinking			0.000	1.000
Yes	50 (100.00)	60 (100.00)		
No	4 (0.00)	8 (0.00)		
Hypertension			0.000	1.000
Yes	54 (100.00)	68 (100.00)		
No	0 (0.00)	0 (0.00)		
Disease type			1.395	0.498
Prostate adenocarcinoma	53 (98.15)	66 (97.06)		
Squamous carcinoma	1 (1.85)	2 (2.94)		
Small cell carcinoma	0 (0.00)	0 (0.00)		
T staging			0.000	0.991
T0-T2	4 (7.41)	5 (7.35)		
T3-T4	50 (92.59)	63 (92.65)		
N staging			1.105	0.293
N0	6 (10.91)	12 (17.65)		
N1	49 (89.09)	56 (82.35)		
M staging			0.564	0.453
M0	7 (12.73)	12 (17.65)		
M1	48 (87.27)	56 (82.35)		

with the ELISA test kits' instruction manuals (Shanghai Tongwei Industrial Co., Ltd). Finally, we used an enzyme-labeled analyzer to determine the OD value of each well at the 450 nm wavelength and calculated the TNF-α, IL-1β and IL-6 levels.

Statistical methods

SPSS 19.0 (Beijing Bizinsight Information Technology Co., Ltd.) was used for the statistical analysis. The count data were expressed as the number of cases/percentage [n (%)] and analyzed using chi-squared tests, and the measurement data were represented by the mean ± standard deviation ($\bar{x} \pm s$). The comparisons between groups at the same time point were analyzed through independent-samples t tests, and the comparisons before and after within a group were analyzed using paired t tests. When the *P* value was less than 0.05, a difference was considered statistically significant.

Results

General clinical data of patients in groups A and B

There were no significant statistical differences in the general clinical data between groups A and B (P>0.05) (**Table 1**).

Pain relief effects of patients in the two groups during the treatment

(1) Pain relief rate. The pain relief rates of the two groups increased from 1 month to 12 months after they finished taking the medication (P<0.001). Among them, the rates of those in group A treated for 1 month, 6 months, and 12 months were dramatically higher than of the rates in group B (P<0.001) (**Figure 1**).

(2) VAS scores. The VAS scores of the patients in the two groups from 1 month to 12 months after they stopped taking the medication were all decreased (P<0.001). The patients' scores in group A at 1 month, 6 months, and 12 months after they started taking the medication were dramatically lower than the scores in group B (P<0.001) (**Figure 2**).

Changes in the patients' serum-related indexes in the two groups

(1) Changes in immune function-related indexes of the patients in both groups. There were no significant differences in the serum $CD4^+$, $CD8^+$, $CD4^+/CD8^+$ and $CD3^+$ levels in the two groups 1 month after they started taking the medication (P>0.05). The $CD4^+/CD8^+$ levels in both groups were down-regulated at 12 months after they started taking the medication (P<0.001). The $CD4^+/CD8^+$ levels in group A at 6 months and 12 months after the patients started taking the medication were dramatically lower than they were in group B (P<0.001).

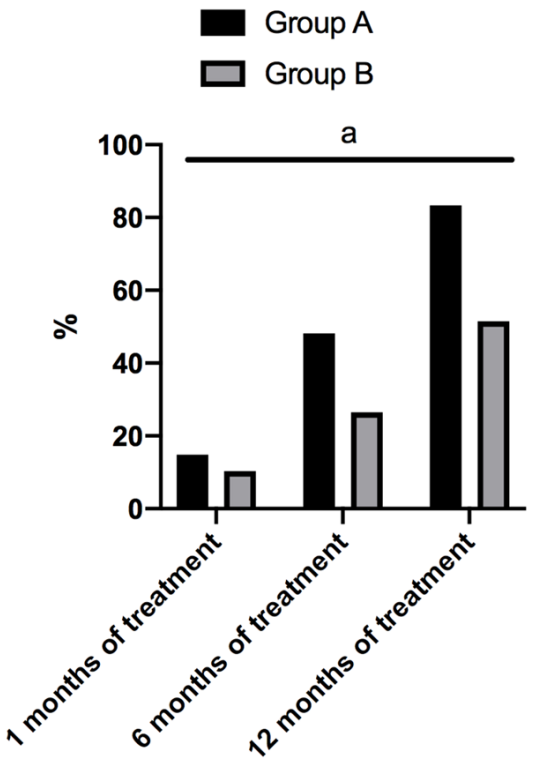

Figure 1. Pain relief rates of the patients in the two groups during their treatment. Note: a means P<0.001.

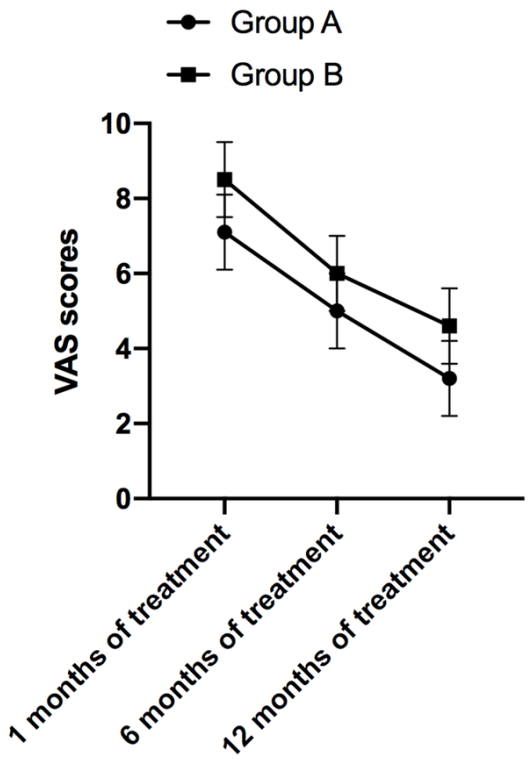

Figure 2. The VAS scores of the patients in the two groups during their treatment. Note: a means P<0.001.

The $CD4^+$, $CD8^+$ and $CD3^+$ levels in both groups were increased at 12 months after they started taking the medication (P<0.001). The $CD4^+$, $CD8^+$ and $CD3^+$ levels in group A at 6 months and 12 months after they started taking the medication were dramatically higher than they were in group B (P<0.001) (**Figure 3**).

(2) Changes in inflammatory reaction-related indexes in both groups of patients. There was no marked difference in the serum TNF-α, IL-1β, or IL-6 levels between the two groups at one month after they started taking the medication (P>0.05). The TNF-α, IL-1β, and IL-6 levels in both groups were all decreased at 12 months after they started taking the medication (P<0.001). The TNF-α, IL-1β, and IL-6 levels in group A at 6 months and 12 months after they started taking the medication were dramatically lower than they were in group B (P<0.001) (**Figure 4**).

(3) Changes in prostate-specific antigen indexes of the patients in both groups. The PSA and F-PSA of the patients in the two groups from 1 month to 12 months after they started taking the medication were both down-regulated (P< 0.001). The PSA and F-PSA levels of the patients in group A treated for 1 month, 6 months, and 12 months showed no significant differences (P>0.05) (**Figure 5**).

Medication safety in both groups

(1) Side effects of the drugs. There were no significant differences between the two groups in the incidence of gynecomastia, breast tenderness, diarrhea, nausea, or temporary liver function changes during the treatment (P>0.05) (**Table 2**).

(2) Adverse reactions. There were no marked differences in the incidence of renal calculus, osteoporosis, anemia, or other adverse reactions between both groups (P>0.05) (**Table 3**).

Comparison between clinical efficacy of groups A and B

The total effective rate of the patients in group A (94.44%) was significantly higher than the rate in group B (70.59%) (**Table 4**).

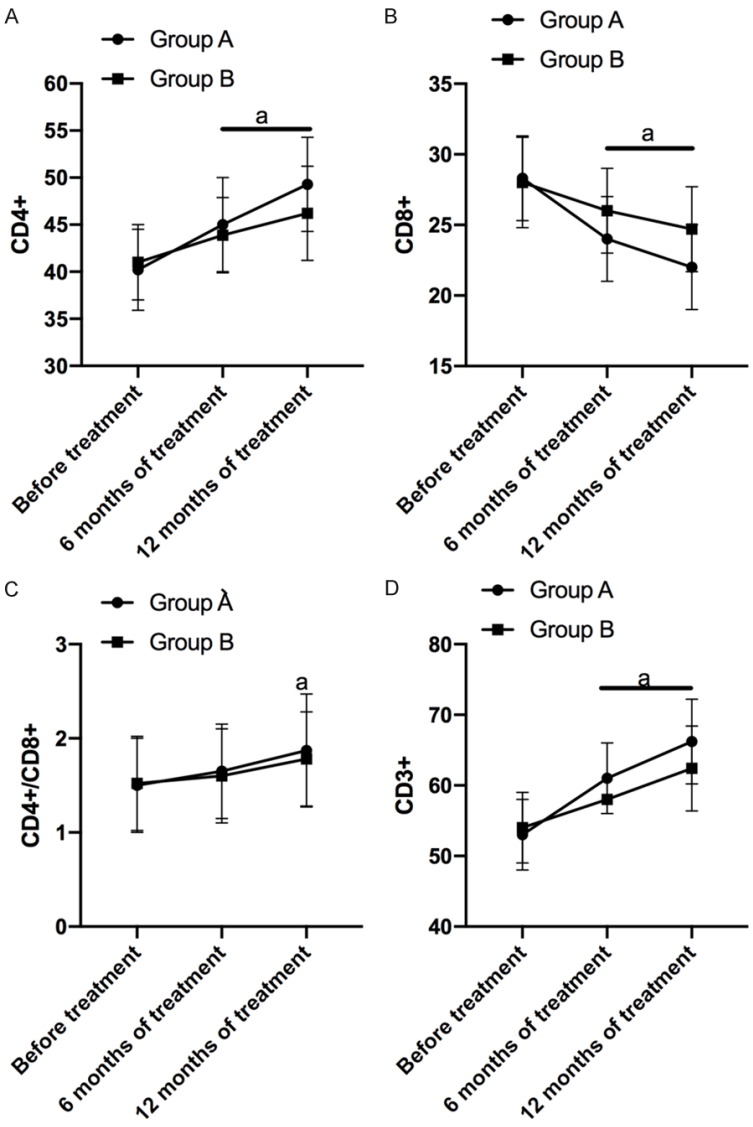

Figure 3. The immune function-related indexes of the patients in the two groups. A: Serum $CD4^+$ content. B: Serum $CD8^+$ content. C: Serum $CD4^+$/$CD8^+$ content. D: $CD3^+$ content in the serum. Note: a means $P<0.001$.

Discussion

The etiology of prostate cancer is complex, and the patients' ages, genetic factors, and lifestyles play a role [19]. With the advances in research on the molecular mechanisms of cancer, a large number of studies have confirmed that patients' immune systems and their own inflammatory reactions all affect disease conditions [20, 21]. Abnormal immune function is a vital link in inducing disease progression. Prostate cancer patients have abnormal immune function and regulating the body's immune function can inhibit prostate cancer [22]. How to improve the immune function of the body while improving the patients' clinical efficacy is the focus of clinical endocrine therapy [23].

In this research, we first compared the visual pain relief effects of the patients in the two groups during treatment and found that the pain relief rates of those treated with an intermittent therapy of goserelin and bicalutamide for 1 month, 6 months and 12 months were dramatically higher than the rates of those treated with a continuous therapy of goserelin and bicalutamide. Some related studies show that both goserelin and bicalutamide can relieve the pain symptoms of cancer patients to some extent, and the advantages of the intermittent therapy schemes of goserelin and bicalutamide lie in reducing the drug dosage and treatment costs [24]. Next, we observed the changes in the immune function, inflammatory response and prostate-specific antigen indexes of the patients in both groups. $CD4^+$, $CD8^+$ and $CD3^+$ are marker molecules on the surface of mature T cells, and $CD8^+$ is a marker of inhibitory molecules of T cells [25]. The results indicated that the $CD4^+$/$CD8^+$ levels of the patients in both groups were decreased and the $CD4^+$, $CD8^+$ and $CD3^+$ levels were increased. The $CD4^+$/$CD8^+$ levels of the patients in group A at 6 months and 12 months after the medication were significantly lower than they were in group B, and the $CD4^+$, $CD8^+$ and $CD3^+$ levels were dramatically higher than they were in group B. Research has confirmed that abnormal immune function is a vital link in inducing the onset of prostate cancer. T lymphocytes, are an important cell for the body to complete the cellular

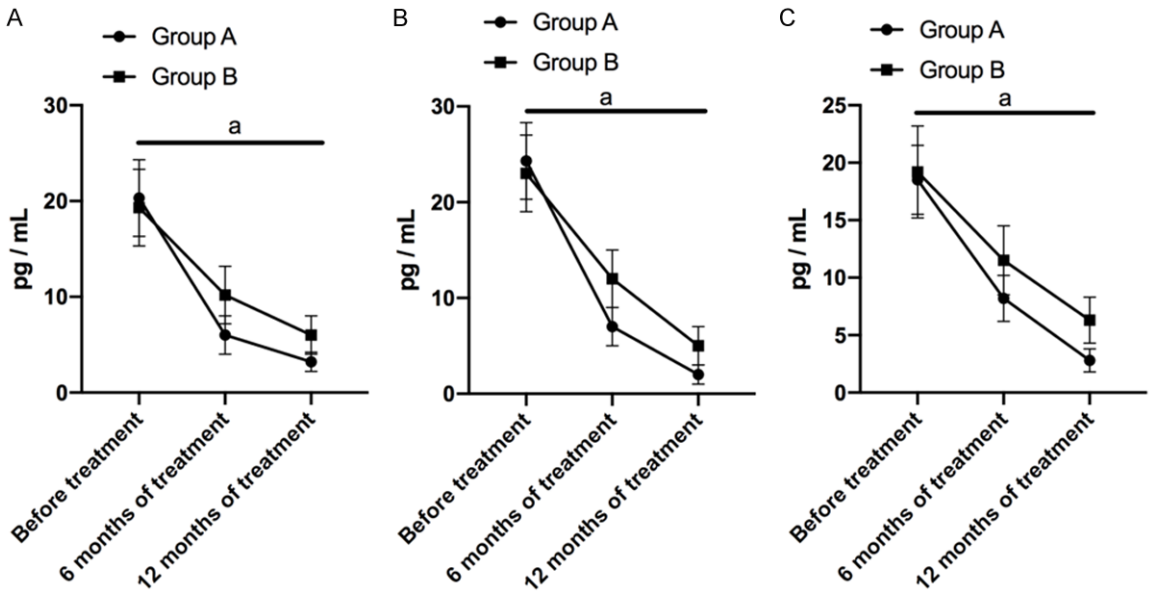

Figure 4. The inflammatory reaction-related indexes of the patients in the two groups. A: Serum TNF-α content. B: Serum IL-1β content. C: Serum IL-6 content. Note: a means P<0.001.

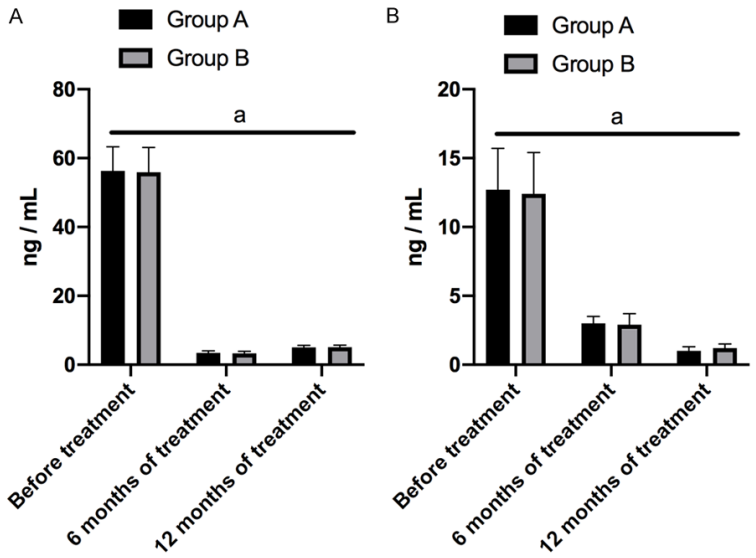

Figure 5. Changes in the prostate-specific antigen indexes of the patients in the two groups. A: Serum PSA content. B: Serum F-PSA content. Note: a means P<0.001.

immune response, they play a crucial part in correcting immune function disorders in the body [26]. In combination with this study, we believe that both therapeutic schemes have good immunoregulatory effects on prostate cancer patients. The prostate-specific antigen index, the PSA, and the F-PSA in both groups were significantly decreased, and the differences between the PSA and F-PSA levels were not statistically significant. PSA and F-PSA are important screening indicators for prostate cancer. Many studies have confirmed that the two are abnormally high in prostate cancer [27]. The TNF-α, IL-1β, and IL-6 inflammatory factor levels of the patients under intermittent therapy were decreased more than those receiving continuous treatment. Inflammation is relevant to the occurrence and development of various types of tumors [28]. Over-expressed inflammatory cells induce gene mutations, thus constructing a microenvironment suitable for tumor cell proliferation and tumor growth [29]. TNF-α induces acute phase reactions, directly acts on tumor neovascularization, and indirectly promotes the growth of tumor cells [30]. Endocrine therapy-related studies signify that clinically, the metastatic sites of patients with lymph node metastasis of prostate cancer are often tissues over-expressing IL-1β and IL-6 [31]. Therefore, we believe that goserelin com-

Table 2. Side effects of the drugs

Group	Group A (54)	Group B (68)	X^2	P
Gynecomastia	1 (1.85)	2 (2.94)	-	-
Breast tenderness	4 (7.41)	7 (10.29)	-	-
Diarrhea	7 (12.96)	10 (14.71)	-	-
Nausea	8 (14.81)	9 (13.24)	-	-
Temporary liver function changes	1 (1.85)	2 (2.94)	-	-
Total incidence	21 (38.89)	30 (44.12)	0.338	0.561

Table 3. Adverse reactions

Group	Group A (54)	Group B (68)	X^2	P
Renal calculus	2 (3.70)	2 (2.94)	-	-
Osteoporosis	3 (5.56)	4 (5.88)	-	-
Anemia	6 (11.11)	10 (14.71)	-	-
Total incidence	11 (20.37)	16 (23.53)	0.174	0.676

Table 4. Treatment efficacy in both groups

Group	Group A (54)	Group B (68)	X^2	P
Complete remission	28 (51.85)	23 (33.82)	-	-
Partial remission	15 (27.78)	15 (22.06)	-	-
Mild remission	8 (14.81)	10 (14.71)	-	-
No relief/progress	3 (5.56)	20 (29.41)	-	-
Total effective rate of treatment	51 (94.44)	48 (70.59)	11.200	0.001

bined with bicalutamide therapy can improve immune function and relieve the inflammatory response in patients with advanced prostate cancer. The effect of intermittent therapy is better. Finally, we analyzed the clinical efficacy and safety of patients in both groups during treatment. There was no statistically significant difference in the incidence of side effects such as gynecomastia, breast tenderness, diarrhea, nausea, temporary liver function changes, or adverse reactions such as kidney stones, osteoporosis and anemia during treatment. The total effective rate of the patients in group A was significantly higher than it was in group B. Due to drug reactions, it is difficult to avoid adverse reactions when administering long-term medication. In contrast, the principle of the intermittent therapy scheme of goserelin combined with bicalutamide aims to reduce the hormone dosage, the side effects of the corresponding drugs, and the incidence of adverse reactions.

In this study, we carefully observed the pain relief effects, changes in the serum-related indexes, the drug side effects, and the patients' adverse reactions during treatment. However, we lack the data to perform comparisons with the routine clinical serum biochemical indexes and the supplemental data relating to the patients' health and economic conditions. We will pay attention to the latest results of relevant research in the later stages and hope that these research results can be referred to and supplemented.

Conclusion

Goserelin combined with bicalutamide can improve the clinical efficacy of treating patients with advanced prostate cancer. Meanwhile, it improves their immune function and relieves the body's inflammatory response, so it is worthy of clinical application.

Disclosure of conflict of interest

None.

Address correspondence to: Chenglin Xiao, Department of Urology, The Second Affiliated Hospital of Guangzhou Medical University, No. 250, Changgang East Road, Haizhu District, Guangzhou 510260, Guangdong Province, China. Tel: +86-020-39195875; E-mail: xiaobvkgixf3709@163.com

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